Docket No: 20481/0206417-US0

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Per Holm and Tomas Norling

Serial No.: 10/513,807 Art Unit: 1615

Confirmation No.: 7864

Filed: November 8, 2004 Examiner: Melissa S Mercier

For: SOLID DOSAGE FORM COMPRISING A FIBRATE

DECLARATION OF DR. REZA FASSIHI
PURSUANT TO 37 C.F.R. §1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

I, Reza Fassihi, Ph.D., declare as follows:

1. I am currently a Professor of Biopharmaceutics and Industrial Pharmacy at Temple University, School of Pharmacy, a position I have held for 17 years. I received a bachelors in pharmacy from Punjab University in India with first class honors, and a Ph.D. in Pharmaceutics from Brighton University, School of Pharmacy, in Brighton, England. I have authored or co-authored more than 130 peer-reviewed papers, and am a Fellow of the American Association of Pharmaceutical Scientists (AAPS). I am a named inventor on seven

U.S. patents, six of which are directed to drug delivery systems and one directed to a method and apparatus for dissolution testing of a dosage form. A copy of my curriculum vitae is attached as Exhibit 1. I have more than 30 years experience designing, preparing, and testing pharmaceutical formulations. Much of my research has focused on formulations of poorly soluble drugs, such as fenofibrate. In fact, I have co-authored a technical note regarding the potential effect of sink conditions on dissolution properties of fenofibrate (*J. of APPS PharmSci. Tech.* 7(2):Article 33 (2006)).

2. I have reviewed the above-identified patent application, the February 17, 2009 Office Action, and the references cited therein (namely, Koretke (WO 01/95939), Parikh (US 7,255,877), Grouiller (US 4629624), and Breitenbach (US 6350398)). I make this declaration in support of the present application.

3. I understand that the pending claims stand rejected as obvious over Koretke (WO 01/95939) in view of Parikh (US 7,255,877) and, for some claims, Grouiller (US 4629624) and Breitenbach (US 6350398).

4. There are a large number of drugs (in excess of 30% of all marketed pharmaceutical products) that are poorly soluble or insoluble as defined by the U.S. Pharmacopoeia (USP) and the Biopharmaceutical Classification System (BCS) (class II and IV drugs).

5. Absorption of an orally administrable drug is necessary to make it bioavailable. Poor drug solubility can significantly decrease absorption of the drug resulting in decreased bioavailability, increased chance of food effect, and unpredictable variations among individuals with respect to bioavailability. BCS divides drugs into four classes: class I (highly permeable,

highly soluble), II (highly permeable, poorly soluble), III (poorly permeable, highly soluble), and IV (poorly soluble, poorly permeable). In general, class I drugs provide for predictable and high bioavailability, while class II and IV drugs exhibit poor and unpredictable bioavailability due to poor solubility. Ideally, one would like to transform the solubility characteristics of class II drugs (poorly soluble) into class I drugs in order to have predictable and high bioavailability. It should be noted that among many drugs that qualify as class II drugs, fenofibrate is one example.

6. Poor drug solubility can be due to a number of factors including crystal structure, intermolecular forces, the presence of hydrophilic, hydrophobic, and other chemical groups in the drug molecule, particle size, polarity, drug lipophilicity, melting point, and molecular weight.

7. There are more than a dozen methods by which a poorly soluble drug may be solubilized; the effectiveness of these methods depends on numerous factors including the drug's chemical structure and molecular configuration. Some examples of theses techniques include micronization, salt formation, solid dispersions, self emulsifying systems, supercritical fluid techniques, nanoparticles, complexation with cyclodextrin, pH adjustment, salting in and/or salting out, prodrugs, liposomes, lyophilization, wet milling, co-crystal formation, lipids, and the use of surfactants, lipids, and co-solvents,. Additionally, each technique has many parameters that can vary and may have to be adjusted depending on the characteristics of the drug.

8. As yet, there is no single method of solubilization that can apply universally to all poorly soluble drugs. There are numerous methods that have been described in the

literature and patents that are not suitable for scale-up and/or robust enough for commercialization for many poorly soluble drugs. The ability of these methods to solubilize a drug is highly specific to a particular drug, its physicochemical and mechanical properties, and the dose (e.g., 50 mg or 1000 mg) in the dosage form. For example, complexation by cyclodextrin requires a specific molecular volume of the drug as the drug must fit within the cavity provided by the cyclodextrin. There are only a few marketed drugs that satisfy this requirement.

9. Due to the complexity of solubilization, a skilled formulator cannot scientifically predict whether a given method will successfully and sufficiently solubilize a specific drug or not. Therefore, extensive experimentation is often required to solubilize a particular drug. The end result of which is unpredictable and may or may not be of value.

10. Koretke prepares a solid dispersion by co-melting of the drug, poloxamer surfactant, and polyethylene glycol (PEG), followed by filling of the molten material into capsule shells or molds and allowing the material to cool (p. 6, lines 32-38). The gradually cooled material will be non-uniform (heterogeneous) as much of the drug will sediment to the bottom of the capsule shell or mold. Koretke specifically distinguishes its hot fill method from prior known methods of forming solid dispersions: "This property distinguishes this invention from known solid dispersion dosage forms in which [the] solid dispersion of drug and PEG were milled and filled into capsules or tableted" (page 6, lines 36-38).

11. Koretke's co-melt material does not lend itself to the formation of tablets. The material is designed to be filled into a capsule shell or mold in a hot melt form (page 6, lines 30-32). Solidification occurs in the shell or mold. The co-melt material contains at least 60%

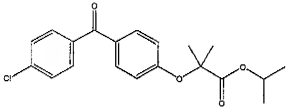
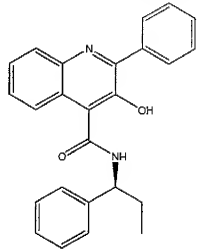
PEG rendering it unsuitable for tabletting due to the large proportion of PEG relative to other components, and sticking of the waxy, low melting point PEG material to the tabletting equipment. During tabletting, the PEG would be expected to melt under typical compression and frictional forces of the tabletting machine (from about 1000-3000 kg), stick to the die and punches, and not be ejectable from the machine.

12. The applicant's method includes spray drying a mixture of the fenofibrate, poloxamer, and PEG onto a solid carrier (such as lactose, a commonly used compressible excipient for tabletting). Unlike Koretke, the resulting particles can be sieved, blended, lubricated, and compressed into tablets on a conventional tabletting machine for high speed production (see, e.g., Example 1 of the present appplication).

13. The formulation in Koretke is also not suitable for commercialization. Tablets are manufactured routinely at a rate of about 3000-4000 tablets per minute, while capsules containing powder materials are typically manufactured at a rate of about 200-300 capsules per minute on large scale capsule filling machines. In contrast, hot melt filling of formulations into capsules (such as described in Koretke) is generally not commercially viable due to the rate of dosage form production (typically <200 capsules per minute) and difficulty in controlling content uniformity and stability (both are requirements for USP and the U.S. Food and Drug Administration (FDA)). Variations in content uniformity is attributed to temperature variations and viscosity changes during processing and filling, and consequently fill volume.

14. Koretke discloses the formulation of a quinoline compound using its hot fill method. As shown by the table below, fenofibrate and the quinoline compound have significantly different physicochemical properties. As such, a skilled formulator would not

know whether Koretke's hot fill method could be used to successfully formulate a highly bioavailable fenofibrate formulation. By the same token, a skilled formulator would have the same difficulty in formulating fenofibrate by other known techniques of solubilization.

Fenofibrate	(S)-(-)-N-(α-ethylbenzyl)-3-hydroxy-2-phenylquinoline-4-carboxamide
	
Melting point: 79-82° C	122-125° C[1]
clogP: 5.24[2]	7.38

15. Based on my experience, fenofibrate is a particularly difficult drug to formulate and achieve a high and reproducible rate of dissolution. This is shown by the fact that Abbott Laboratories has re-formulated its fenofibrate formulation at least twice. Its original 200 mg fenofibrate capsules were re-formulated as 160 mg fenofibrate tablets, which are bioequivalent to the 200 mg fenofibrate capsules. See Exhibit 2. The 160 mg tablets were re-formulated as 145 mg tablets. See Exhibit 3. The 145 mg tablets are bioequivalent under fed conditions to the 200 mg fenofibrate capsules.

[1] The melting point for (S)-(-)-N-(0-ethylbenzyl)-3-hydroxy-2-phenylquinoline-4-carboxamide is reported in WO 95/32948 (see compound 85 on page 46).

[2] The clogP values for both compounds was calculated using ChemDraw Ultra 11.

16. In my opinion, based on my more than 30 years of experience in the field of pharmaceutical formulations, a formulation scientist would not have reasonably expected that the presently claimed delivery system would be significantly more effective at delivering fenofibrate than other systems for delivering poorly soluble drugs, such as those used in the commercialized 200 mg, 160 mg, and 145 mg fenofibrate formulations. These results are unexpected.

17. I further declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements are made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under §1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the instant application or any patent issued thereupon.

9/22/09
Date

Reza Fassihi, Ph.D.

Exhibit 1

Biography

Reza Fassihi, B Pharm., Ph.D., AAPS Fellow
Professor of Biopharmaceutics and
Industrial Pharmacy

Dr. Fassihi is a professor of biopharmaceutics and industrial pharmacy at Temple University, school of pharmacy where he has taught and done research in the pharmaceutical sciences. He received his B.S. in pharmacy and his Ph.D. in Pharmaceutics from Brighton University in England in 1978 and was awarded a gold medal for his research work. He has worked as an assistant professor (1979-1982), a postdoctoral fellow at Brighton University (1983), a Senior Scientist at Welsh School of Pharmacy (1984), Senior Lecturer at Rhodes University in South Africa (1984-1986), and has been Professor and Chair of Department, and head of school of pharmacy, University of the Witwatersrand in Johannesburg (1986-1992) where he was awarded with gold medals by both the Academy of Pharmaceutical Sciences of South Africa and the Society of Cosmetic Chemists.
In 1991 he was a visiting professor at Cincinnati University and in 1992 he joined Temple University where he has served as professor, director of graduate programs, has chaired various committees and is Co-chair of PPF (Philadelphia Pharmaceutical Forum). He has been an invited speaker at various professional meetings and pharmaceutical industries and has presented seminars and workshops nationally and internationally and is a member of numerous societies.
Dr. Fassihi has authored or coauthored more than 125 peer-reviewed professional papers on topics related to the relationship between the physicochemical characteristics of formulations and their biological effect, with an emphasis on design, development, evaluation, optimization and scale up operations of oral dosage forms and controlled drug delivery. He has numerous chapters in books, holds 6 US patents and has over 350 abstracts. He is a member of several professional organizations including the AACP, ACS, HPA, AAPS and CRS and is a Fellow of AAPS.
He has trained 22 MS and PhD students and has mentored visiting scholars and postdoctoral fellows. Dr. Fassihi's research involves the study of the special problems of the various routes of administration of particular Drug Delivery System from a physicochemical, physiological, biopharmaceutical and mechanistic viewpoint.
He acts as consultant to pharmaceutical and government agencies, and has served as an expert witness on development and use of drugs and issues related to pharmaceutical products.

CURRICULUM VITAE

Reza Fassihi, B. Pharm., Ph.D., HPA, AAPS Fellow

Addresses for Correspondence:

Work: **Temple University**
School of Pharmacy
3307 N. Broad Street
Philadelphia, PA 19140
(215) 707-7670 - FAX: (215) 707-3678
e-mail: reza.fassihi@temple.edu

Home: **352 Dreshertown Road**
Fort Washington PA 19034
Telephone # 215-283-0261
Cell phone # 215-680-3120

Employment and Positions Held:

1992-present	Professor of Biopharmaceutics and Industrial Pharmacy, Temple University, School of Pharmacy, Philadelphia, PA.
Sept.1995 to Jan. 1998	Director of Graduate Research and Studies, Temple University , School of Pharmacy
Sept. 1991 to Sept. 1992	Visiting Professor, University of Cincinnati, Medical Center, College of Pharmacy, Cincinnati, OH.
1988-1992	Head, School of Pharmacy and Professor of Pharmaceutical Sciences, Faculty of Medicine, University of the Witwatersrand, Johannesburg, South Africa.
1984-1988	Senior Lecturer, School of Pharmaceutical Sciences, Rhodes University, Grahamstown , South Africa

Oct. 1983 - Oct. 1984	Senior Scientist, Welsh School of Pharmacy, UWIST, Cardiff, U.K.
June 1982 - July 1983	Postdoctoral Fellowship, School of Pharmacy, Brighton University, England.
Feb. 1979- 1982	Asst. Professor of Pharmaceutics, School of Pharmacy, Isfahan University, Isfahan.

Honors

Award of Gold Medal for the best Ph.D. graduate in Pharmaceutics, School of Pharmacy, Brighton University, Brighton, England (1978).

Award of Medal from South African Academy of Pharmaceutical Sciences (1991).

Award of Medal from Society of Cosmetic Chemist (1991).

AAPS Fellow Status (2003).

Award for outstanding contribution by the FDA , "Symposium on Controlled Release of Solid Oral Dosage Forms", September 2002.

AAPS Award for outstanding contribution to AAPS student chapters.

Distingushed Speaker Award by the EPTM (eastern pharmaceutical technology meeting), New Jersey ,September 2005.

Major Academic Qualifications:

1978	Doctor of Philosophy degree (Ph.D.) in Pharmaceutics from the School of Pharmacy, Brighton University, Brighton, England
1974	B. Pharm., First Class Honors , Punjab University , India
1969	Diploma in Natural and Biological Sciences

Membership

Member of the Institute of Physical Sciences in Medicine. IPSM.
Member of Hospital Physicist Association. HPA United Kingdom.
Member of South African Academy of Pharmaceutical Sciences.
Member of Society of Cosmetic Chemists of South Africa.

Member of American Association of Pharmaceutical Scientists. AAPS.
Member of Controlled Release Society. CRS.
Member of American Association of Colleges of Pharmacy. AACP.

Research Experience

Biopharmaceutics and physicochemical aspects of preformulation / formulation / scale-up and design of drug delivery systems to include solid dosage forms, controlled release formulations, drug absorption and GI constraints, microbiological evaluation of pharmaceuticals, topical formulations and percutaneous drug absorption, optimization of dissolution methodologies for novel drug dosage forms and delivery system evaluations, in-vitro/in-vivo correlation research and bioavailability / bioequivalency issues.

Courses taught at Post Graduate and Pharm.D. levels

Pmarmaceutical manufacturing (preformulation and formulation development)– Part-I, 3 credit course.

Pharmaceutical Manufacturing (product development, scale-up operations)- Part-II, 3 credit course.

Applied Biopharmaceutics (drug absorption, bioavailability and bioequivalency, in-vitro-in vivo correlations)- 3 credit course.

Pharmaceutical dosage forms- 3 credit course.

Pharmaceutics and Biopharmaceutics, 4 credit course.

Dermatopharmaceutics- 3 credit course.

Wound healing and surgical dressings- 2 credit elective course.

Administrative Experience and Responsibilities:

1988-1992	Head, School of Pharmacy, University of Witwatersrand, and Johannesburg, South Africa. Responsible for overall activities and management of school.
1988-1992	Chairman, Department of Pharmaceutics at Witwatersrand University.
1993- 1998	Member of Graduate Board at Temple University. (TU).

1993-Present Co-Chairman of Education Committee, at Philadelphia Pharmaceutical Forum.

1993-1994 Member of Fellowship Committee, Temple University.

1994-1996 Member of Nominating Committee, Temple University.

1995-1998 Member of Students Appeal Committee.

1995 – 1998 Director of Graduate Studies in the School of Pharmacy, Temple University.

1995-2002 Official Representative to the USP 1995 - 2000 General Committee of Revision

1996-Present Member of Protocol Review Committee of NIH for Pharmaceutical projects.

1986-Present Consultant to various pharmaceutical drug manufacturers.

1990- present Expert witness on issues related to pharmaceutical products; patent infringements, consulting on manufacturing processes, and technical problems. Have been deposed and appeared at the trials on numerous occasions.

Inventions:

1. REZA FASSIHI,
   "Method and Apparatus for Dissolution Testing of A Dosage Form.".
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2. REZA FASSIHI and L. Yang
   "Controlled release drug delivery system"
   US patent # 5783212 issued in July 21, 1998.

3. REZA FASSIHI AND VINESS PILLAY
   Monolithic Tablet for controlled drug release
   US Patent # 6090411, issued July-2000.

4. REZA FASSIHI and H. Kim
"Matrix for controlled delivery of highly soluble pharmaceutical agents"
US patent # 6337091 B1; issued Jan. 8, 2002.

5. REZA FASSIHI AND T. DURIG
"Amino acid modulated extended release dosage form"
US patent # 6,517,868 B2; issued Feb. 11, 2003.

6. R. Fassihi and T. Dürig. Amino Acid Modulated Extended Release Dosage Form. **US Patent # 6936275 B2, August 30th ,2005.**

7. REZA FASSIHI AND V. PILLAY
Compressed composite delivery system for release-rate modulation of bioactives.
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8. **R.Fassihi and T. Durig.**
"Amino acid modulated extended release dosage form".
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2. A. R. FASSIHI and I KANFER: **Chapter 16**: The effect of compressibility and powder flow properties on tablet weight variation; in Pharmaceutical Technology, Tableting Technology, M. H. Rubinstein, John Wiley & Sons, UK (1987) pp 189-202.

3. A. R. FASSIHI.
Preservation of medicines against microbial contamination, in: **Chapter 50**: 4th. Edition ; Disinfection, Sterilization and Preservation;
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4. REZA FASSIHI

Preservation and Microbiological Attributes of Non-Sterile Pharmaceutical Products, **Chapter 64**: In 5th Edition of Disinfection, Sterilization and Preservation; Ed. Seymour S. Block, Ph.D. Lippincott Williams and Wilkins 2000 ,pp 1263-1281.

5. A. R. FASSIHI, P. J. DAVIES and M. S. PARKER.
Inimical effects of compression on survival of spores.
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6. A. R. FASSIHI, P. J. DAVIES and M. S. PARKER.
Effect of punch pressure on the survival of fungal spores during the preparation of tablets from contaminated raw materials
Zbl. Pharm. Heft.12; vol.116, 1267-1272, (1977).

7. A. R. FASSIHI and M. S. PARKER.
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8. A. R. FASSIHI and MALCOLM S. PARKER.
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9. A. R. FASSIHI and M. S. PARKER.
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10. A. R. FASSIHI, M. S. PARKER and D. DINGWALL.
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11. A. R. FASSIHI and MALCOLM S. PARKER.
The influence of compaction pressure upon pore size and surface structure of tablets and their consequent moisture relationship.
Acta Pharmaceutica Technologica; Supplement7; pp. 65-70 (1979).

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Drug Development and Industrial Pharmacy, 6 (5), 441-450 (1980).

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14. A. R. FASSIHI, M. S. PARKER and N. POURKAVOOS.
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17. A. R. FASSIHI.
Compression characteristics of polymers in tablet formulations.
5th. Int. Pharm. Tech. Conference, Harrogate, England (1986), Vol II: 222-227.

18. A. R. FASSIHI and M. S. PARKER,
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5th. Int. Pharm. Tech. Conference, Harrogate, England pp 97-111, (1986).

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Compressibility and powder flow properties.
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International Journal of Pharmaceutics, 37 (1987) 119-125.

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46. A. R. FASSIHI and S. S. D. ROBERTSON.
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47. D. L. MUNDAY, A. R. FASSIHI and C. DeVILLIERS.
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50. M. DANCKWERTS and A. R. FASSIHI.
Implantable controlled release drug delivery systems.
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53. W. A. RITSCHEL, N. N. VACHHARAJANI, H. FORUSZ and A. R. FASSIHI.
On the Mechanism of effect of fatty acids on gastric emptying.
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54. REZA FASSIHI AND L.M. OSMAN
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55. J. M. HAIGH, E. W. SMITH, E. MEYER and R. FASSIHI..
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121. Quan Liu, Reza. Fassihi
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Development Of A Robust Once A Day Glipizide Matrix System
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123. R. Talukder, and R. Fassihi
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Journal of Pharmacy and Pharmacology; 60: 1297-1303 (2008).

124. Rahmat M. Talukder, Yunqi Wu, Shahla Jamzad and Reza Fassihi
Drug solubility character and release from controlled release polymer based matrices: An analysis of front(s) movement on dissolution rate (submitted).

125. Quan Liu, Yunqi Wu and Reza Fassihi
Development and evaluation of a swellable and floatable gastro-retentive delivery system (submitted).

126. Quan Liu, Reza Fassihi
Comparative study of swelling and erosion properties of PEO, HPMC and Kollidon SR (submitted).

127. Q.Liu, E. Lee, and Reza Fassihi
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Talks and Presentations:

More than 350 presentations and published abstracts at various national and international meetings including scientific conferences, workshops, seminars, universities and government agencies during the past 23 years.

Abstracts and Invited Lectures

Papers have been presented at the following meetings on a regular basis:
1. AAPS 5th to Present annually on a regular basis.
2. Controlled Release Society every year since 1990.
3. British Pharmaceutical Conference on a regular basis.
4. Regional AAPS Meetings since 1990 every year.

Recent Presentations at national meetings, conferences, pharmaceutical companies and government agencies (partial list) as an invited speaker:

1. **"In-vitro-in-vivo correlation (IVIVC) challenges for modified release formulations".**
   Reza Fassihi Ph.D.
   Glatt Air Techniques, CR Symposium Sept.18 th -20th ,2007, Ramsey, New Jersey
2. **Current challenges and future of modified release product development**
   Reza Fassihi Ph.D.
   Colorcon North American MR Forum Program, May 9-10 2007.
3. **Development of a sensitive and reliable dissolution procedure:Unconventional drug delivery systems**
   Reza Fassihi Ph.D.
   ACS Mid-Atlantic Regional Meeting May 16-18; 2007, Ursinus College, Collegeville, PA.

4. **Reza Fassihi- Eastern New Jersey pharmaceutical Technology meeting, Advances in controlled release hydrophilic systems. September 16th ,2005.**
5. **Reza Fassihi- FDA, Philadelphia, District, PA –April 23-27, 2004.**
   "Theory and Concepts of Specialized Dissolution Analysis".

6. **Invited speaker at the 2004 AAPS Annual Meeting and Exposition November 7-11, 2004 at the Baltimore Convention Center, Maryland.**
   Presentation title: "Physicomechanical characterization of different polymeric materials and core substrates employed in formulation of film-coated dosage forms".

7. Invited speaker at Modified release Forum, Colorcon, Philadelphia, April 22-23, 2004. " Matrix type Controlled release systems- Recent advances".

8. **Invited speaker at the 2003 AAPS Annual Meeting and Exposition October 26-30, 2003 at the Salt Palace Convention Center, Utah. Presentation title:** "Understanding release fromhydrophilic matrices- towards a functional characterization of old and new polymers".

9. **Invited speaker at CRS 2003 Workshop, July 2003, Glasgow ,Scotland**
Modified release products and challenges in oral delivery
Presentation title: "In-vitro dissolution assessment of swelling, erosing matrices".

10. **Presentation at Astra-Zeneca, April 2003, Willmington DE, Novel Drug Delivery Technologies :** "An Integrated Approach Based on New Formulation Strategies".

11. **Reza Fassihi- BMS, May, 1st , 2003**
Trend in Controlled Release Delivery Technologies and manfacturing.

12. **Reza Fassihi- DuPont, Advance Drug Delivery, Development, Manufacturing and In-vitro-In-vivo Evaluation of Hydrophilic Matrix Systems. March 19, 2003.**

13. **Reza Fassihi- Sanofi-Synthelabo Inc., PA, Techniques of Solubilization: Class II Drugs. June 2002.**

14. **Reza Fassihi- FDA- Office of Generic Drugs, "Symposium on Controlled release of Solid Oral Dosage Forms" September 23-24, 2002.**
Hydrophilic Matrix Technologies for Controlled Release Drug Delivery.

15. **Reza Fassihi- Colorcon Inc, PA,**
Modified Release Academic Forum North American Program

October 2002.
"In-vitro assessment of slow release drug delivery systems".

16. Reza Fassihi- Scolr Inc. Redmond ,WA
Role of Amino Acids in Solubilization of Poorly Soluble drugs. June 2002.

17. Reza Fassihi- Penwest Company in NY,
Unconventional dissolution methods for release rate determination from swellable hydrophilic matrices. December 2001.

18. Reza Fassihi- Scolr Inc. Redmond ,WA
Electrolytes and Their Effects on Matrix Behavior. June 2001.

19. Reza Fassihi- Hercules Incorporated; Aqualon Division; Wilmington, DE 19894; April 6th 2001.
Rational Approaches to Drug Delivery Design for Adding Value to Drug Product: New strategies and use of Hydrophilic Swellable Polymers".

20. Reza Fassihi- R&D group at GSK (GlaxoSmithKline), King of Prussia, PA, 19406. January 24th 2001
Novel Approaches for Oral-Controlled Release delivery Systems".

21. Reza Fassihi- GlaxoSmithKline, Sterile Product group, King of Prussia, PA, August 7th 2000.
Moisture Induced Phase Transition in Amorphous Systems: Cefazolin Sodium".

22. Reza Fassihi- Prometheus Laboratory, San Diego, CA 92121; June 10th 2000,
"Three layer technology for multiple drug therapy in H.Pylori related Ulcer".

23. Reza Fassihi- Delsys Pharmaceutical Corporation; Monmouth Junction, NJ 08852; July 15th 2000
"Unconventional Dissolution Study of Floatable and Sticking Hydrophilic Swell able Delivery systems".

24. Reza Fassihi- Union Carbide Corporation, Bound Brook, NJ 08805, April 15th, 1999.

"Electrolyte-Induced Compositional Heterogeneity in a Tablet Matrix for Rate-Controlled Drug Delivery".

25. Reza Fassihi- Andrx Pharmaceutical Inc. FL, November 1999 "Matrix Technologies and Formulation Design Parameters for Controlled Release Delivery".

26. Reza Fassihi- McNeil Consumer Healthcares, Tablets: Formulations; Evaluation and Optimization. October 1998.

27. Reza Fassihi- GlaxoSmithKline, PA Formulation Development for Controlled Release Delivery of Drugs; September 1999.

28. Reza Fassihi- Eurand Inc., OH, Advances in Current Modified Release Delivery Technologies. July 1998.

29. Reza Fassihi- Prometheus Laboratories, San Diego CA, Design and Development Triple layer Tablet for Multiple Drug Delivery in the Upper GI Tract. December 1998.

30. Reza Fassihi- Delsys Pharmaceuticals- Elan, NJ, Drug Deposits/membrane and dissolution methods, August 1998.

31. Reza Fassihi- Verion Inc., Easton PA, Class I and II Drugs: Formulation Challenges. September 1999.

32. Reza Fassihi- Scolr Inc. Redmond ,WA Challenges in the Development of Sustained Release Dosage Forms. April 2000.

33. Reza Fassihi- Pfizer CT, Biopharmaceutics and Pharmacokinetics Considerations in Product development. Two days seminar, July, 1998.

34. Reza Fassihi- SugarLoaf Conference Center, Philadelphia PA, Three Days Symposium, Trends in controlled release technologies and solid dosage forms, May 11- 13, 1994.

35. Reza Fassihi- Eastern New Jersey pharmaceutical Technology meeting, Advances in controlled release hydrophilic systems. September 16th ,2005.

36. **Reza Fassihi- AAPS , Atlanta Georgia World Congress Center, Nov. 16, 2008, Invited spearker, - Title of presentation-"Utilization of drug-buffer-polymer interactions for modified release of pH-sensitive drugs".**

Recent presentations (past 6 years) at annual meetings of American Pharmaceutical Association.

1. **Evaluation of crosslinked calcium-alginate, calcium-pectinate and calcium-alginate-pectinate pellets for site-specific drug delivery** Viness Pillay, Reza Fassihi (AAPS 1998, San Francisco, CA)

2. **A new method for dissolution studies of lipid-filled hard shell or softgel capsules.** Viness Pillay, Reza Fassihi (AAPS 1998, San Francisco, CA)

3. **Comparing the Dynamics of Matrix Densification Associated with HPMC and PEO Systems**
   Viness Pillay, B. Johnson, Reza Fassihi (AAPS 2000, Indianapolis, IN)

4. **Role of Lubrication Efficiency on Release Reproducibility from Dry Blend and Wet Granulated Low Drug Load Tablets.**
   R. M. Talukder, R. Fassihi, M. I. Johnson (AAPS 2001, Denver, CO)

5. **The Compactability of a Direct Compression Controlled Release Oral Solid Dosage Form Using Polyethylene Oxide.**
   M. S. Karetny, R. Fassihi (AAPS 2001, Denver, CO)

6. **Unconventional Dissolution Method for Determination of Glucosamine from Sustained Release Matrix.**
   Y. Wu, R. Fassihi (AAPS 2001, Denver, CO)

7. **Low Cost High-Load Monolithic Controlled Release Oral Delivery System for Nutraceuticals.**
   M. P. Hite, C. A. Federici, S. J. Turner, R. Fassihi (AAPS 2001, Denver, CO)

8. **Development of a High Drug Load Monolithic Controlled Release Oral Delivery System for Niacin: A Novel Approach.**
   M. P. Hite, C. A. Federici, S. J. Turner, R. Fassihi (AAPS 2001, Denver, CO)

9. **Novel Design of a Cost-Effective Monolithic Controlled Release Decongestant.**
M. P. Hite, C. A. Federici, S. J. Turner, R. Fassihi (AAPS 2001, Denver, CO)

10. **Textural and Torque-based Procedure to Determine the Degree of Powder Mixing and Lubrication Efficiency for Scale-up Tableting.**
C. V. Navaneethan, S. Missaghi, R. Talukder, M. Johnson, R. Fassihi (AAPS 2001, Denver, CO)

11. **Application of a Dual Crosslinking Reaction for Development of a Multiple-Unit Binary Polymeric System Designed for Constant Drug Release Rate.**
V. Pillay, N. Hurbans, C. M. Dangor, R. Fassihi (AAPS 2001, Denver, CO)

12. **Statistical Optimization Applied in Formulation of Novel Superswelling Crosslinked Polyvinylalcohol Matrices.**
V. Pillay, P. Danckwerts, R. Fassihi (AAPS 2001, Denver, CO)
13. **Extrusion-Spheronization Technology for Development of New HPMC-Based Spherules**
V. Pillay, D. Lutchman, C. M. Dangor, D. Perumal, R. Fassihi (AAPS 2001, Denver, CO)

14. **Development Of Controlled Release Hydrophilic Matrix Tablets For Topical Colonic Delivery Of 5-aminosalicylic Acid**
Rahmat Talukder, Reza Fassihi (AAPS 2002, Toronto, ON)

15. **Stability Analysis Of Granulated Metronidazole And Tetracycline HCl By HPLC**
Yunqi Wu, Reza Fassihi (AAPS 2002, Toronto, ON)

16. **Assessment of Film Formation On Different Tablets Using Texture Analysis And Confocal Laser Scanning Microscopy**
Shahrzad Missaghi, Reza Fassihi (AAPS 2002, Toronto, ON)

17. **Design And Development Of A Controlled Release Formulation For "dissolution-rate Limited" Dimenhydrinate Via In-situ Interactions Of Charged Substances And Polymers**
Shahrzad Missaghi, Reza Fassihi, Stephen John Turner (AAPS 2002, Toronto, ON)

18. **A Novel In Situ Solubilization For A 'dissolution Rate Limited' Drug Within The Hydrophilic Matrix For Controlled Release Delivery:**

Ondansetron Hydrochloride
Charu V Navaneethan, Reza Fassihi, Stephen John Turner (AAPS 2002, Toronto, ON)

19. **In-situ Solubilization of Class II Drugs During The Hydrosol-gelation Phase In The Presence Of Amphoteric Amino Acids, Polysaccharides, And Polymers: A Novel Approach In Controlled Release Drug Delivery**
Reza Fassihi, Thomas Durig, Stephen John Turner (AAPS 2002, Toronto, ON)

20. **Novel Design Of A Monolithic Oral Controlled-release Delivery Formulation For Novasoy® Soy Isoflavone Concentrate**
Stephen John Turner, Cathy Federici, Mike Hite, Reza Fassihi (AAPS 2002, Toronto, ON)

21. **Novel Design Of A Robust And Rugged Oral Monolithic Controlled Release Delivery System For Tramadol Hydrochloride.**
Stephen John Turner, Mike Hite, Cathy Federici, Reza Fassihi (AAPS 2002, Toronto, ON)

22. **In Vivo – In Vitro Correlation (IVIVC) Of A Novel Monolithic Controlled Release Dosage Form**
Stephen John Turner, Mike Hite, Cathy Federici, Reza Fassihi (AAPS 2002, Toronto, ON)

23. **Influence Of Excipients And In-situ Ph Variation On Release Kinetics Of Metronidazole And Tetracycline Hydrochloride From A Matrix Tablet**
Yunqi Wu, Reza Fassihi (AAPS 2003, Salt Lake City, UT)

24. **Swelling And Erosion Characterization Of HPMC and PEO Tablets During Dissolution**
Yunqi Wu, Reza Fassihi (AAPS 2003, Salt Lake City, UT)

25. **Influence Of Polyethylene Oxide Molecular Weight On Release Kinetics Of A Class-ii Drug: 4-androstene-3,17-dione**
Rahmat M. Talukder, Reza Fassihi (AAPS 2003, Salt Lake City, UT)

26. **Evaluation And Comparison Of Dissolution Profiles For A Swelling And Eroding Dimenhydrinate Tablet Using Usp Apparatus I, II, And III**
Shahrzad Missaghi, Reza Fassihi (AAPS 2003, Salt Lake City, UT)

27. **Simulation Of Gastrointestinal Contractile Forces On Release Kinetics Of Swelling/eroding Matrices**
Majde Takieddin, Reza Fassihi (AAPS 2003, Salt Lake City, UT)

28. **Effect Of Non-ionizable Soluble And Insoluble Excipients On Release Kinetics From Hpmc Based Tablets**
Shahla Jamzad, Lara Tutunji, Reza Fassihi (AAPS 2003, Salt Lake City, UT)

29. **Development And Dissolution Kinetic Studies Of Ondansetron Hydrochloride From Hydrophilic Matrices Of Polyethylene Oxide**
Charu V Navaneethan, Reza Fassihi (AAPS 2003, Salt Lake City, UT)

30. **Design And Development Of A Gastroretentive Delivery System For Upper Gastrointestinal Tract Drug Delivery**
Yunqi Wu, Reza Fassihi (AAPS 2003, Salt Lake City, UT)

31. **Formulation Development Of A Novel Self-correcting Controlled Release Matrix System Incorporating Film-forming Polymer Coatings**
Michael Patrick Hite, Steven Turner, Catherine Federici, Reza Fassihi (AAPS 2003, Salt Lake City, UT)

32. **In Vitro Investigations Of Alternative Controlling Polymer Formulations Of A Novel, Self-correcting Controlled Release Matrix Displaying Ba/be To A Reference-listed Product**
Michael Patrick Hite, Steven Turner, Catherine Federici, Reza Fassihi (AAPS 2003, Salt Lake City, UT)

33. **Novel Design of An Oral Monolithic Controlled Release Delivery System For Branded Active Materials**
S. J. Turner, C. Federici, M. Hite, R. Fassihi (AAPS 2003, Salt Lake City, UT)

34. **Development of a monolithic matrix tablet for glipizide: Analysis of drug release and induction of lag-time**
Shahla Jamzad, Reza Fassihi (AAPS 2004, Baltimore, MD)

35. **Physicomechanical characterization of different polymeric materials and core substrates employed in formulation of film-coated dosage**

forms
Shahrzad Missaghi, Reza Fassihi (AAPS 2004, Baltimore, MD)

36. **Design and development of a microporous modified release verapamil tablet: analysis of linearity and lag time**
Shahrzad Missaghi, Reza Fassihi (AAPS 2004, Baltimore, MD)

37. **Porosity-controlled osmotic system for delivery of high-load niacin with complete release and absence of burst effect**
Charumathy Navaneethan, Reza Fassihi (AAPS 2004, Baltimore, MD)

38. **Evaluation of drug release and performance parameters for metformin commercial tablets**
Lara Tutunji, Reza Fassihi (AAPS 2004, Baltimore, MD)

39. **Development of a delivery system with controlled onset and release rate for targeting distal intestine and colon**
Rahmat Talukder, Reza Fassihi (AAPS 2004, Baltimore, MD)

40. **Stressed stability studies of granulated metronidazole, tetracycline HCl, famotidine and colloidal bismuth subcitrate**
Yunqi Wu, Reza Fassihi (AAPS 2004, Baltimore, MD)

41. **Development of a tri-layered gastroretentive delivery system for the treatment of H. pylori associated ulcer**
Yunqi Wu, Reza Fassihi (AAPS 2004, Baltimore, MD)

42. **Interactive Functions of Moisture Content, Lubricant, and Physical Character of Excipients on Ejection Force and Tensile Strength**
Quan Liu, Shahla Jamzad, Shahrzad Missaghi, Charumathy Navaneethan,
Reza Fassihi (Nashville, TN, 2005)
43. **Analysis of Matrix Geometry and Front Movements for Hydroxypropyl Methyl Cellulose (HPMC), Hydroxypropyl Cellulose (HPC), and Polyethylene Oxide (PEO)**
Shahrzad Missaghi, Reza Fassihi (Nashville, TN, 2005)

44. **Design and Development of a Stable Oral Dosage Form of Omeprazole, an Acid-Labile Model Drug, via Compression and Enteric Coating**
Shahrzad Missaghi, Reza Fassihi (Nashville, TN, 2005)

45. **Synchronization of swelling, erosion, and release in a novel and robust formulation of glipizide**
Shahla Jamzad, Reza Fassihi (Nashville, TN, 2005)

46. **Dissolution rate of BCS Class II drugs: Influence of pH, surfactants, and sink condition on discriminatory power of dissolution testing**
Shahla Jamzad, Reza Fassihi (Nashville, TN, 2005)

47. **Compatibility study of metformin and selected polymers using differential scanning calorimetry and FTIR spectroscopy**
Lara Tutunji, Reza Fassihi (Nashville, TN, 2005)

48. **Development of a dual coated (rupturable) matrix system for targeting distal intestine and colon**
R.Talukder and Reza Fassihi,
AAPS (American Association of Pharmaceutical Scientists)
Annual meeting October 29-November 2, 2006, San Antonio, TX

49. **Development and in-vitro dissolution study of alfuzosin hydrochloride extended-release composite formulation**
Q. Liu and R. Fassihi
AAPS (American Association of Pharmaceutical Scientists)
Annual meeting October 29-November 2, 2006, San Antonio, TX

50. **Preformulation characterization of Glipizide as a low-dose drug in controlled release drug delivery**
S. Jamzad and R. Fassihi
AAPS (American Association of Pharmaceutical Scientists)
Annual meeting October 29-November 2, 2006, San Antonio, TX

51. **Comparative evaluation of physico-mechanical characteristics of gelatin and hypromellose capsules**
S. Missaghi and R. Fassihi
AAPS (American Association of Pharmaceutical Scientists)
Annual meeting October 29-November 2, 2006, San Antonio, TX

52. **Current challenges and future of modified release product development**
Reza Fassihi Ph.D.
2007 Colorcon North American MR Forum Program, May 9-10 2007.

53. **Development of a sensitive and reliable dissolution procedure:Unconventional drug delivery systems**
Reza Fassihi Ph.D.
ACS Mid-Atlantic Regional Meeting May 16-18; 2007, Ursinus College, Collegeville, PA.

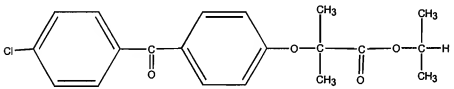
54. **"In-vitro-in-vivo correlation (IVIVC) challenges for modified release formulations".**
Reza Fassihi Ph.D.
Glatt Air Techniques, CR Symposium Sept.18 th -20th ,2007, Ramsey, New Jersey.

TRICOR®
(fenofibrate tablets)

R_x Only

DESCRIPTION

TRICOR (fenofibrate tablets), is a lipid regulating agent available as tablets for oral administration. Each tablet contains 54 mg or 160 mg of fenofibrate. The chemical name for fenofibrate is 2-[4-(4-chlorobenzoyl) phenoxy]-2-methyl-propanoic acid, 1-methylethyl ester with the following structural formula:



The empirical formula is $C_{20}H_{21}O_4Cl$ and the molecular weight is 360.83; fenofibrate is insoluble in water. The melting point is 79-82°C. Fenofibrate is a white solid which is stable under ordinary conditions.

Inactive Ingredients: Each tablet contains colloidal silicon dioxide, crospovidone, lactose monohydrate, lecithin, microcrystalline cellulose, polyvinyl alcohol, povidone, sodium lauryl sulfate, sodium stearyl fumarate, talc, titanium dioxide, and xanthan gum.

In addition, individual tablets contain:

54 mg tablets: D&C Yellow No. 10, FD&C Yellow No. 6, FD&C Blue No. 2.

CLINICAL PHARMACOLOGY

A variety of clinical studies have demonstrated that elevated levels of total cholesterol (total-C), low density lipoprotein cholesterol (LDL-C), and apolipoprotein B (apo B), an LDL membrane complex, are associated with human atherosclerosis. Similarly, decreased levels of high density lipoprotein cholesterol (HDL-C) and its transport complex, apolipoprotein A (apo AI and apo AII) are associated with the development of atherosclerosis. Epidemiologic investigations have established that cardiovascular morbidity and mortality vary directly with the level of total-C, LDL-C, and triglycerides, and inversely with the level of HDL-C. The independent effect of raising HDL-C or lowering triglycerides (TG) on the risk of cardiovascular morbidity and mortality has not been determined.

Fenofibric acid, the active metabolite of fenofibrate, produces reductions in total cholesterol, LDL cholesterol, apolipoprotein B, total triglycerides and triglyceride rich lipoprotein (VLDL) in treated patients. In addition, treatment with fenofibrate results in increases in high density lipoprotein (HDL) and apoproteins apoAI and apoAII.

The effects of fenofibric acid seen in clinical practice have been explained *in vivo* in transgenic mice and *in vitro* in human hepatocyte cultures by the activation of peroxisome proliferator activated receptor α (PPARα). Through this mechanism, fenofibrate increases lipolysis and elimination of

triglyceride-rich particles from plasma by activating lipoprotein lipase and reducing production of apoprotein C-III (an inhibitor of lipoprotein lipase activity).
The resulting fall in triglycerides produces an alteration in the size and composition of LDL from small, dense particles (which are thought to be atherogenic due to their susceptibility to oxidation), to large buoyant particles. These larger particles have a greater affinity for cholesterol receptors and are catabolized rapidly. Activation of PPARα also induces an increase in the synthesis of apoproteins A-I, A-II and HDL-cholesterol.

Fenofibrate also reduces serum uric acid levels in hyperuricemic and normal individuals by increasing the urinary excretion of uric acid.

Pharmacokinetics/Metabolism

Plasma concentrations of fenofibric acid after administration of 54 mg and 160 mg tablets are equivalent under fed conditions to 67 and 200 mg capsules, respectively.

Absorption

The absolute bioavailability of fenofibrate cannot be determined as the compound is virtually insoluble in aqueous media suitable for injection. However, fenofibrate is well absorbed from the gastrointestinal tract. Following oral administration in healthy volunteers, approximately 60% of a single dose of radiolabelled fenofibrate appeared in urine, primarily as fenofibric acid and its glucuronate conjugate, and 25% was excreted in the feces. Peak plasma levels of fenofibric acid occur within 6 to 8 hours after administration.

The absorption of fenofibrate is increased when administered with food. With fenofibrate tablets, the extent of absorption is increased by approximately 35% under fed as compared to fasting conditions.

Distribution

In healthy volunteers, steady-state plasma levels of fenofibric acid were shown to be achieved within 5 days of dosing and did not demonstrate accumulation across time following multiple dose administration. Serum protein binding was approximately 99% in normal and hyperlipidemic subjects.

Metabolism

Following oral administration, fenofibrate is rapidly hydrolyzed by esterases to the active metabolite, fenofibric acid; no unchanged fenofibrate is detected in plasma.

Fenofibric acid is primarily conjugated with glucuronic acid and then excreted in urine. A small amount of fenofibric acid is reduced at the carbonyl moiety to a benzhydrol metabolite which is, in turn, conjugated with glucuronic acid and excreted in urine.

In vivo metabolism data indicate that neither fenofibrate nor fenofibric acid undergo oxidative metabolism (e.g., cytochrome P450) to a significant extent.

Excretion

After absorption, fenofibrate is mainly excreted in the urine in the form of metabolites, primarily fenofibric acid and fenofibric acid glucuronide. After administration of radiolabelled fenofibrate, approximately 60% of the dose appeared in the urine and 25% was excreted in the feces.

Fenofibric acid is eliminated with a half-life of 20 hours, allowing once daily administration in a clinical setting.

Special Populations

Geriatrics

In elderly volunteers 77 - 87 years of age, the oral clearance of fenofibric acid following a single oral dose of fenofibrate was 1.2 L/h, which compares to 1.1 L/h in young adults. This indicates that a similar dosage regimen can be used in the elderly, without increasing accumulation of the drug or

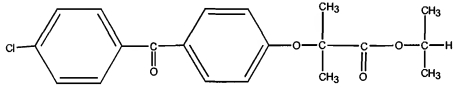
(Nos. 6122, 6123)
NEW

TRICOR® 48 mg and 145 mg
(FENOFIBRATE TABLETS)

R_x Only

DESCRIPTION

TRICOR (fenofibrate tablets), is a lipid regulating agent available as tablets for oral administration. Each tablet contains 48 mg or 145 mg of fenofibrate. The chemical name for fenofibrate is 2-[4-(4-chlorobenzoyl) phenoxy]-2-methyl-propanoic acid, 1-methylethyl ester with the following structural formula:



The empirical formula is $C_{20}H_{21}O_4Cl$ and the molecular weight is 360.83; fenofibrate is insoluble in water. The melting point is 79-82°C. Fenofibrate is a white solid which is stable under ordinary conditions.

Inactive Ingredients: Each tablet contains hypromellose 2910 (3cps), docusate sodium, sucrose, sodium lauryl sulfate, lactose monohydrate, silicified microcrystalline cellulose, crospovidone, and magnesium stearate.

In addition, individual tablets contain:
48 mg tablets: polyvinyl alcohol, titanium dioxide, talc, soybean lecithin, xanthan gum, D&C Yellow #10 aluminum lake, FD&C Yellow #6 /sunset yellow FCF aluminum lake, FD&C Blue #2 /indigo carmine aluminum lake.
145 mg tablets: polyvinyl alcohol, titanium dioxide, talc, soybean lecithin, xanthan gum.

CLINICAL PHARMACOLOGY

A variety of clinical studies have demonstrated that elevated levels of total cholesterol (total-C), low density lipoprotein cholesterol (LDL-C), and apolipoprotein B (apo B), an LDL membrane complex, are associated with human atherosclerosis. Similarly, decreased levels of high density lipoprotein cholesterol (HDL-C) and its transport complex, apolipoprotein A (apo AI and apo AII) are associated with the development of atherosclerosis. Epidemiologic investigations have established that cardiovascular morbidity and mortality vary directly with the level of total-C, LDL-C, and triglycerides, and inversely with the level of HDL-C. The independent effect of raising HDL-C or lowering triglycerides (TG) on the risk of cardiovascular morbidity and mortality has not been determined.

Fenofibric acid, the active metabolite of fenofibrate, produces reductions in total cholesterol, LDL cholesterol, apolipoprotein B, total triglycerides and triglyceride rich lipoprotein (VLDL) in treated

patients. In addition, treatment with fenofibrate results in increases in high density lipoprotein (HDL) and apoproteins apoAI and apoAII.
The effects of fenofibric acid seen in clinical practice have been explained *in vivo* in transgenic mice and *in vitro* in human hepatocyte cultures by the activation of peroxisome proliferator activated receptor α (PPARα). Through this mechanism, fenofibrate increases lipolysis and elimination of triglyceride-rich particles from plasma by activating lipoprotein lipase and reducing production of apoprotein C-III (an inhibitor of lipoprotein lipase activity).

The resulting fall in triglycerides produces an alteration in the size and composition of LDL from small, dense particles (which are thought to be atherogenic due to their susceptibility to oxidation), to large buoyant particles. These larger particles have a greater affinity for cholesterol receptors and are catabolized rapidly. Activation of PPARα also induces an increase in the synthesis of apoproteins A-I, A-II and HDL-cholesterol.

Fenofibrate also reduces serum uric acid levels in hyperuricemic and normal individuals by increasing the urinary excretion of uric acid.

Pharmacokinetics/Metabolism

Plasma concentrations of fenofibric acid after administration of three 48 mg or one 145 mg tablets are equivalent under fed conditions to one 200 mg capsule.

Absorption

The absolute bioavailability of fenofibrate cannot be determined as the compound is virtually insoluble in aqueous media suitable for injection. However, fenofibrate is well absorbed from the gastrointestinal tract. Following oral administration in healthy volunteers, approximately 60% of a single dose of radiolabelled fenofibrate appeared in urine, primarily as fenofibric acid and its glucuronate conjugate, and 25% was excreted in the feces. Peak plasma levels of fenofibric acid occur within 6 to 8 hours after administration.

Exposure to fenofibric acid in plasma, as measured by C_{max} and AUC, is not significantly different when a single 145 mg dose of fenofibrate is administered under fasting or nonfasting conditions.

Distribution

In healthy volunteers, steady-state plasma levels of fenofibric acid were shown to be achieved within 5 days of dosing and did not demonstrate accumulation across time following multiple dose administration. Serum protein binding was approximately 99% in normal and hyperlipidemic subjects.

Metabolism

Following oral administration, fenofibrate is rapidly hydrolyzed by esterases to the active metabolite, fenofibric acid; no unchanged fenofibrate is detected in plasma.

Fenofibric acid is primarily conjugated with glucuronic acid and then excreted in urine. A small amount of fenofibric acid is reduced at the carbonyl moiety to a benzhydrol metabolite which is, in turn, conjugated with glucuronic acid and excreted in urine.

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